# FDA Electronic Submissions Gateway

# User Guide

**May 1, 2006**

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# 1. Introduction

The business of the Food and Drug Administration (FDA) is extremely information intensive. In recognition of this fact and of the potential benefits offered by Information Technology for assisting with the management of information, the FDA has undertaken a number of projects supporting the electronic submission of text and data from the industries it regulates.

One of these projects entails the establishment of an Agency-wide solution [referred to as the FDA Electronic Submissions Gateway (FDA ESG)] for accepting electronic regulatory submissions. The FDA ESG enables the submission of regulatory information for review. The overall purpose of the FDA ESG is to provide a centralized, agency-wide communications point for receiving electronic regulatory submissions, securely. The new Agency Gateway will enable the FDA to process regulatory information through automated mechanisms while it enables:

- A single point of entry for the receipt and processing of all electronic submissions in a highly secure environment.
- Automating current electronic processes such as the electronic acknowledgment of submissions.
- Supporting the electronic Common Technical Document (eCTD).

The electronic submission process is defined as the receipt, acknowledgment, routing, and notification to a receiving Center of the receipt of an electronic submission. In this definition,

- "Receipt" means transfer of a submission from a sender's system to a temporary storage area in the FDA ESG.
- "Acknowledgment" to the sender that the submission was sent from the sender's system and received by the Gateway.
- "Routing" refers to delivering a submission to a Center-level storage area and initiating a load process to place a submission into a Center receiving system
- "Notification" of a submission's arrival is made to those individuals responsible for the Center's receiving system.
- Each of these terms denotes a step in the process of electronic submission delivery, and together, these steps comprise the whole scope of electronic submission delivery.

The FDA ESG is the central transmission point for sending information electronically to the FDA. Within that context, the FDA ESG is a conduit, or "highway", along which submissions travel to reach their final destination. It does not open or review submissions; it merely routes them to the proper destination.

The FDA ESG uses a software application certified to comply with secure messaging standards. The screen graphics provided in the FDA ESG Web Interface sections of this User Guide are from the application.

## 1.1    Objective

The objective of this User Guide is to provide industry participants with information and guidance on how to prepare and send documents through the FDA ESG. See Table 3-2 for a list of submissions that the FDA ESG will accept. This document provides a high-level description of the electronic submission process via the FDA ESG.

# 2.  Overview of the Registration Process

Registering to use the FDA ESG involves a set of sequential steps that are to be conducted for all submitters and types of submissions. The first steps in the process are designed to ensure that the FDA ESG can successfully receive electronic submissions and that the electronic submissions are prepared according to published guidelines. The testing phase is done using the FDA ESG test system. Once the sender has passed the testing phase, an account will be set up allowing the submissions to be sent to the FDA ESG Production System.

The following diagram illustrates the steps in the process. The remaining sub-sections in Section 2 explain each of the steps in turn.

**Figure 2-1: Overview of the Registration Process**

**FDA Test System**                    **FDA Production System**

Apply for a Test
Account

Apply for a
Production
System
Account

Test Account
Setup and Approval

Production System
Account  Setup and
Approval

No

No

Successful?

Successful?

Yes

Yes

Yes

Send a Test
Submission

Send
Submissions to
the Production
System

No

Successful?
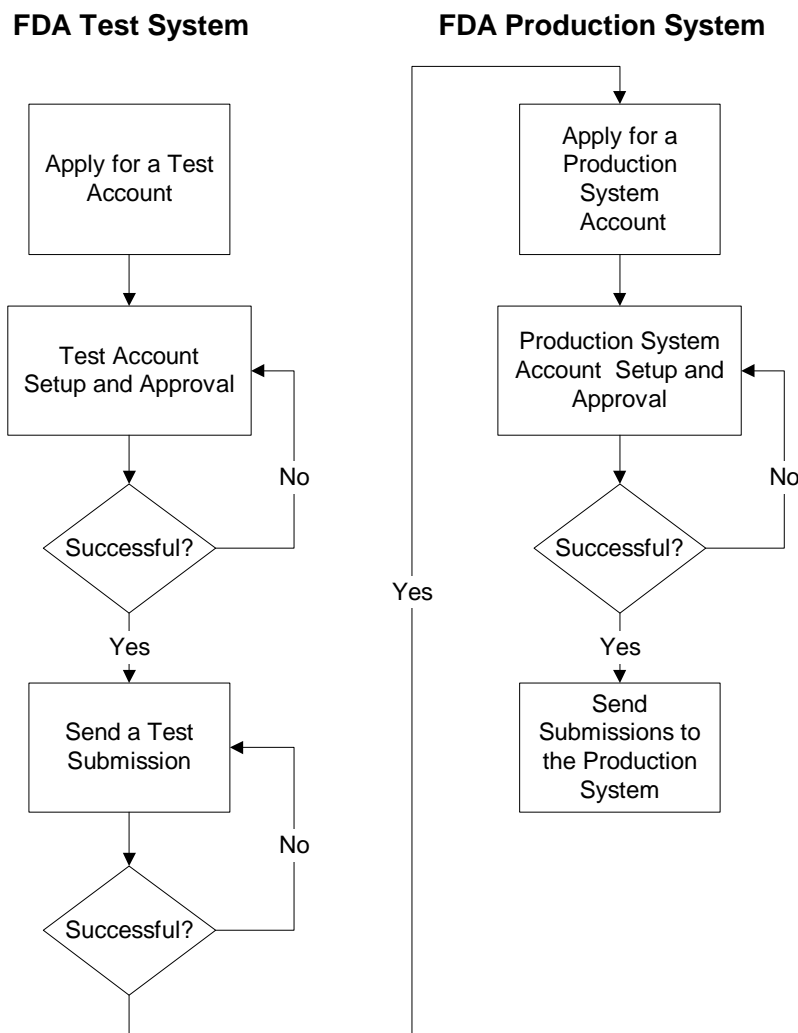
## 2.1    Apply for a Test Account

Organizations that wish to submit electronically to the FDA must apply for an account to establish themselves as Transaction Partners. The term "Transaction Partner" refers to:

> An external entity authorized by the FDA to submit electronic submissions. Authorization includes agreement to regulatory conditions, successful completion of a certification process, and FDA administrative inclusion as a Transaction Partner.

Application for a test account must be initially requested for the FDA ESG. This is done to enable Transaction Partners to send a test submission to the FDA ESG.

Applying for an account involves information-sharing activities between the Transaction Partner and the FDA to set up transmission, receipt, and identification parameters. This ensures the correct identification of the Transaction Partner to the FDA. Digital certificate information is provided to the FDA as part of the application.

## 2.2    Test Account Setup and Approval

The account application is reviewed by the FDA ESG Administrator. The Administrator verifies that a letter of non-repudiation agreement is on file and that the digital certificate conforms to the X.509 version 3 standard and that all data fields in the Issuer and Subject fields are completed (see *Appendix C Digital Certificates* for more information). The Administrator will also communicate with the Transaction Partner to confirm the application information. If these conditions are met, a test account is set up and connections to the FDA ESG test system are established before the submitting organization is approved as a Transaction Partner.

## 2.3    Send a Test Submission

By sending a test submission, the Transaction Partner ensures the following conditions are met:

- The test submission is received by the FDA ESG. A notification is sent by the FDA ESG confirming that the submission was successfully received.
- The submission is routed to the correct Center Holding Area.
- The submission is prepared according to regulatory guidelines. The Center sends an acknowledgement confirming that the submission was prepared correctly.

During the testing process, Transaction Partners who will be sending submissions larger than 1 GB in total size will be asked to send a 7.5 GB test submission. This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery.

## 2.4    Apply for a Production System Account

Applying for a Production System Account in the FDA ESG follows the same process as applying for a test account. Reference *Section 2.1, Apply for a Test Account*.

## 2.5    Production System Account Setup and Approval

The same process is followed to setup a Production System Account as for a Test Account. Reference *Section 2.2, Test Account Setup and Approval.*

## 2.6    Send Submissions to the Production System

After completion of these steps, the Transaction Partner is enabled and approved to send submissions to the FDA ESG. The Production System Account allows the Transaction Partner to send any of the supported submission types to the FDA. **However, the FDA will only process those submission types for which the Transaction Partner has received prior approval.**

**NOTE: It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.**

# 3. Preparatory Activities

There are a number of preparatory activities that need to be completed before beginning the registration process. This section describes these preparatory activities and presents system and protocol issues for FDA ESG users to consider.

## 3.1 Submit Letter of Non-Repudiation Agreement

A letter of Non-Repudiation Agreement must be submitted to the FDA. Reference *Appendix H, Sample Letters of Non-Repudiation Agreement,* for letter examples.

The non-repudiation agreement allows the FDA to receive electronically signed submissions in compliance with 21 Code of Federal Regulations (CFR) Part 11.100.

## 3.2 Obtain Digital Certificate

A digital certificate must be obtained.

Digital certificates ensure private and secure submission of electronic documents. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

Digital certificates can be obtained from either a public or private Certificate Authority (CA). It must be an X.509 version 3 certificate and all data fields in the Issuer and Subject fields must be completed. Reference *Appendix C, Digital Certificates,* for more information on digital certificates.

## 3.3 Understand Submission Guidelines

Each FDA Center has specific guidelines that must be followed for successful submission. Table 3-1 below contains links to Center-specific preparation guidelines and contacts. Table 3-2 lists electronic submissions supported by the FDA ESG.

**Table 3-1: FDA Links to Submission Preparation Guidelines**

| Center | Link |
|---|---|
| Center for Biologics Evaluation and Research (CBER) | http://www.fda.gov/cber/esub/esub.htm |
| Center for Drug Evaluation and Research (CDER) | http://www.fda.gov/cder/regulatory/ersr/default.htm |
| Center for Devices and Radiological Health (CDRH) | http://www.fda.gov/cdrh/cesub.html |
| Adverse Event Reporting System (AERS) | http://www.fda.gov/cder/aerssub/default.htm |

**NOTE: Meeting the requirements for using the FDA ESG to route submissions does not mean that these submissions automatically meet FDA Center-specific submission requirements.**

**For each test submission type, a test submission must be validated by the Center before sending submissions to the Production System.**

**It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.**

**The submission acronyms or names listed in Table 3-2 below are not to be used as attributes in the submission header. See Table G-1 in *Appendix G*, AS2 Header Attributes, for a list of allowed attributes for the different submission types.**

**Table 3-2: Electronic Submissions Supported by the FDA ESG**

| Center | Submissions |
|---|---|
| CBER | AERS – Adverse Event Reports |
| | AERS Attachments |
| | BLA – Biologics License Application (eCTD and eBLA format) |
| | eCTD – Electronic Common Technical Document |
| | IDE – Investigational Device Exemption |
| | IND – Investigational New Drug Application (eCTD and eIND format) |
| | DMF – Drug Master File |
| CDER | AERS – Adverse Event Reports |
| | AERS Attachments |
| | ANDA – Abbreviated New Drug Application |
| | BLA – Biologics License Application (eCTD and eBLA format) |
| | eCTD – Electronic Common Technical Document |
| | NDA – New Drug Application (eCTD and eNDA format) |
| | IND – Investigational New Drug Application |
| CDRH | Adverse Events |
| | Electronic Submissions |

## 3.4    Naming Conventions

A special consideration applies to the naming convention for files and directories. The following characters are not recommended for use when naming submission files and directories:

/ - forward slash

\ - backslash

: - colon

? - question mark

" - quotation marks

< - less than sign

> - greater than sign

| - vertical bar,

space - If you need to use a space, use_an_underscore_instead or
SeparateWordsWithCapitalLetters.

## 3.5    Determine Submission Method

There are three options for sending FDA ESG submissions:

- FDA ESG Web Interface – The FDA ESG Web Interface sends submissions via Hyper Text Transfer Protocol Secure (HTTPS) through a web browser according to Applicability Statement 2 (AS2) standards.

- Applicability Statement 1 (AS1) Gateway-to-Gateway – An electronic submission protocol that uses secure email for communications; and

- Applicability Statement 2 (AS2) Gateway-to-Gateway – An electronic submission protocol that uses HTTP/HTTPS for communications.

Determining the best of these options for your organization will be influenced by the types of submissions to be transmitted, infrastructure capabilities, and business requirements.

One or more of these options can be selected to submit electronic documents to the FDA. However, a separate registration will be required for each option selected.

Considerations for each option are shown in Table 3-3 below.

**Table 3-3: Considerations for Submission Protocol Choice**

| Transaction Partner Considerations | FDA ESG Web Interface | AS1 Gateway-to-Gateway | AS2 Gateway-to-Gateway |
|---|---|---|---|
| **Cost** | None | High setup and support costs | High setup and support costs |
| **Setup** | Minimal | Need to install and configure Gateway | Need to install and configure Gateway |
| **User-friendly web interface** | Yes | No | No |
| **Submission types supported** | All, including AERS reports | AERS Reports and AERS Attachments only | All, including AERS reports |
| **Long-term support by FDA** | Yes | This particular protocol will be phased out in May 2007 | Yes |
| **Preparation of multi-file submissions \*** | Occurs automatically | Not applicable | Multi-file submissions need to be archived and compressed using a tar and gzip utility prior to submission |
| **Custom attributes for submission routing \*\*** | Automatically adds custom attributes to the | Not applicable | Need to add custom attributes to the AS2 |

| Transaction Partner Considerations | FDA ESG Web Interface | AS1 Gateway-to-Gateway | AS2 Gateway-to-Gateway |
|---|---|---|---|
| | AS2 header | | header |
| **Integration to backend systems** | No | Can be automated | Can be automated |
| **Tracking of submission activity by Transaction Partner** | Manual tracking | Can be automated | Can be automated |
| **Automation of submission process** | No | Yes | Yes |

\* See *Appendix B, Creating tar Files and Compressing Files for Submission*

\*\* See *Appendix G, AS2 Header Attributes*

A factor that determines how quickly a submission can be sent to the FDA ESG is the Transaction Partner's network connection to the Internet. Table 3-4 lists the maximum transmission rates for a variety of network connections and the optimal time it would take to send a 1 GB submission.

**Table 3-4: Transmission Rates for Network Connections and Optimal Times for Transmission**

| Network Connection | Max. Transmission Rate (Mbps) | Time (min) |
|---|---|---|
| | | 1 GB |
| T1 | 1.54 | 83 |
| T2 | 6.31 | 21 |
| T3 | 44.7 | 3 |
| OC1 | 51.8 | 2.5 |
| OC3 | 155.4 | 0.8 |
| T4 | 274.8 | 0.5 |
| OC12 | 621.6 | 0.2 |

Mbps = Megabits per sec.

1 GB (Gigabyte) = 8,590 Megabits

Actual times will be greater than those listed in the table due to factors such as network configuration and the amount of traffic coming in and going out through the line. For example, submissions sent in the middle of the day typically take 1.5 – 2 times longer to send than those sent after business hours.  Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG.  These companies had T3 network connections or better.  FDA recommends that submissions of this size be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

During the testing process, Transaction Partners who will be sending submissions larger than 1 GB in total size will be asked to send a 7.5 GB test submission.  This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery.

## 3.6    Connection Requirements

FDA ESG Web Interface users need the following:

- A high-speed internet connection.

- A web browser, either Internet Explorer 6 (or later) or Mozilla Firefox 1.0 (or later).

- Hard disk space of at least three times the size of the submission. For instance, if the submission is 1MB in size, then at least 3MB of hard disk space is required.

- Sun's Java Runtime Edition (JRE) 1.4.2_08, for the browser plug-in files. Reference *Appendix D, Java Runtime Edition Installation* for more information on obtaining and installing JRE.

   Gateway functionality is optimized with JRE version 1.4.2_08 installed.  It is recommended that the automatic Java update option on the computer be disabled to avoid the automatic installation of a different version of JRE.  The steps to do this are as follows:

   1. Select Control Panel from the Start menu.
   2. Double click on the Java (or Java Plug-In) icon.
   3. Click on the "Update" tab.
   4. Uncheck the "Check for Updates Automatically" checkbox.
   5. Click OK.

Gateway-to-Gateway users need the following:

- A high-speed internet connection,

- An AS1 and AS2 compliant Gateway product,

- Hard disk space of at least three times the size of the submission.

   **NOTE: Only Adverse Event Reporting System (AERS) submissions can be sent using the AS1 protocol. All other types of submissions, including AERS, can be sent using the AS2 protocol.**


## 3.7    Help and Information

There are resources that can be contacted if you need assistance with various aspects of the submission process. These are provided in the table below.

**Table 3-5: Submission Process Aspects and Help and Information Contacts**

| Submission Process Aspect | Contact |
|---|---|
| Preparation/Registration/Policy Questions | email: esgprep@fda.gov |
| Technical Issues with Submissions after becoming a Production System Transaction Partner | FURLS Help Desk: 1-800-216-7331, available 7:30 am–11:00 pm, EST www.cfsan.fda.gov/~furls/helpf2.html (this website also contains an email link) |

| Center-specific Submission Guidance | Reference *Section 3.3, Understand Submission Guidelines.* |
|---|---|

# 4. FDA ESG Web Interface Electronic Submissions

The steps for the electronic submission process for FDA ESG Web Interface users are provided in the following sections.

## 4.1    Apply for a Test Account

Applying for an FDA ESG Web Interface Test account is a multi-step process. Before beginning the process, the following information should be known:

- Company and contact information
- Digital Certificate file location

The FDA ESG Web Interface address and a temporary Login ID and password can be obtained from the FDA ESG Administrator by sending an email to esgprep@fda.gov indicating intent to register for the FDA ESG.

The remainder of this section describes the FDA ESG Test Account Application process using screenshots from the FDA ESG Web Interface.

1. Using the address provided by the FDA, access the FDA ESG Web Interface.

   The **Login** page is displayed. Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not continue. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.gov to request access to the test environment.

2.  Enter the **User ID** and **Password** that was provided by the FDA and click the **Login** button.

    The **Welcome to the WebTrader registration wizard** page is displayed. This wizard guides the Transaction Partner through the remainder of the application process.
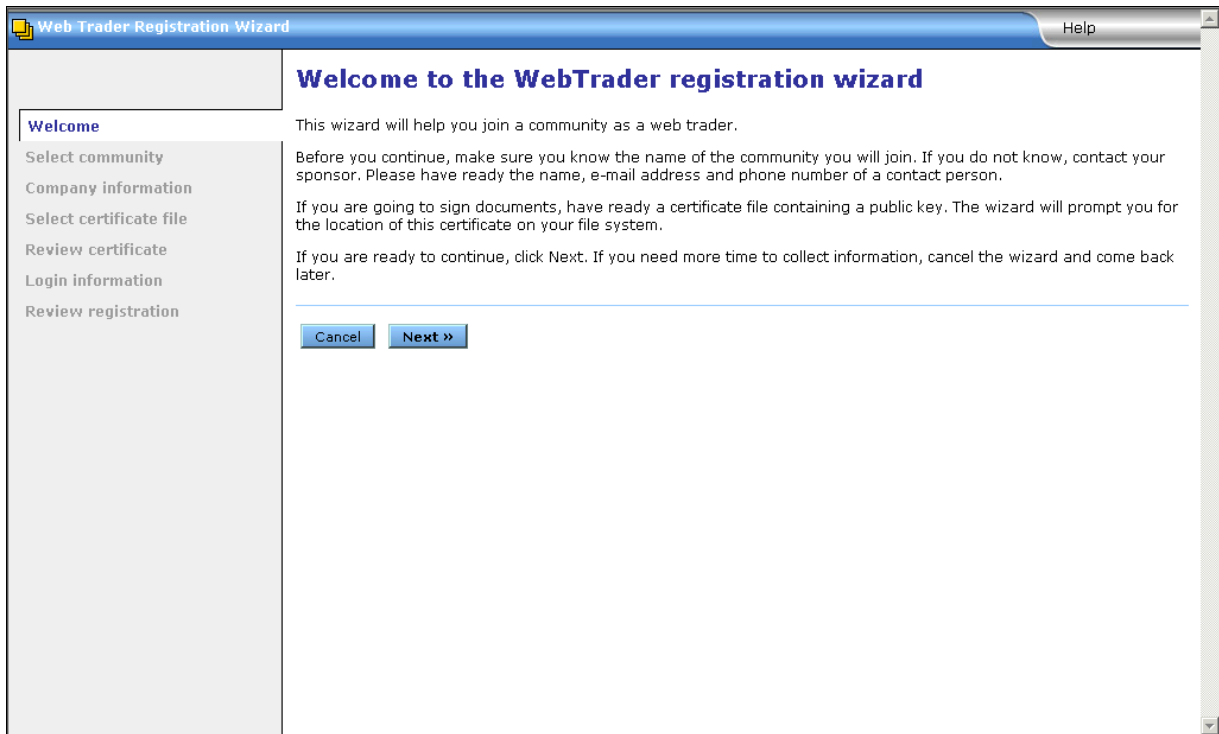
3.  Click the **Next** button.

    The **Pick a Community** page is displayed

    On this page a community is chosen. The community represents where submissions will be sent for logging, verification, and ultimately routing to the appropriate FDA Center. The only community will be the "FDA ESG".

    Reference *Appendix E, Glossary of Terms*, for more information about the community.

4.  Click the **Next** button.

    The Enter company information page is displayed.

    This page records the company name, the primary contact and an alternate contact. This information is necessary for identification so that submission acknowledgements and notifications can be sent to the correct recipient.



5.  Enter the following company information:

    - Company name
    - Primary contact name
    - Primary contact phone
    - Primary contact email
    - Alternate contact name
    - Alternate phone
    - Alternate email

Information must be entered in all fields.

**NOTE: Partners who have either an AS1 or AS2 account already, must enter a unique string (different from the one used when registering for the AS1 or AS2 account) in the Company name field. This is to ensure that this account is treated as a separate identity in the database.**

6.  Click the **Next** button.

The **Locate the certificate file** page is displayed.

This page is used to specify the location of the certificate file. Each submission must be accompanied by a certificate.   The digital certificate must be an X.509 version 3 certificate.

Reference *Appendix C*, Digital Certificates for more information about digital certificates.



**NOTE: There are situations when a valid certificate is not accepted by the registration module and an error message is returned. If this occurs, zip the certificate file and email it to the FDA ESG administrator at esgprep@fda.gov. Once received, FDA will assess the certificate and send a response.**

7.  Provide the desired digital certificate file in the **Certificate file** field by entering the name of the certificate or browsing for one on your hard drive by clicking on the **Browse...** button.

The **View certificate details** page is displayed.

This page is used to review the certificate information and to assign a name to the certificate.  Carefully review the "Issuer" and "Subject" fields to be sure that all data fields are completed (i.e., for each data element such as "CN", there is a value that follows the equals sign).

8.  Click **Next**.

The **Enter login information** page is displayed.

This page is used to specify the login User ID and Password selected by the Transaction Partner. After registration is complete, this User ID and Password will be used by the Transaction Partner to log on to the FDA ESG Web Interface.



9.  Enter a new login User ID and Password. Remember this User ID and Password – it will be used for subsequent Logins.

**NOTE: Any alphanumeric string may be entered in the User ID and Password fields.**

10. Click **Next**.

The **Registration summary** page is displayed.

This final page provides an account summary.



11. Check the **I hereby certify that the information provided herein is true and that I am authorized to register with the FDA** checkbox.

12. Click the **Finish** button to return to the **Login** page, or close the browser window.

## 4.2    Test Account Setup and Approval

After successful Test Account setup, the FDA sends an email to the email address provided for the contact, indicating approval as a Transaction Partner and authorization to send a test submission. Typically, the approval notification is sent on the next business day.

The test submission cannot be sent until this notification has been received.

Java Runtime Edition (JRE) must be installed to send a submission. Reference *Appendix D, Java Runtime Edition Installation* for the installation procedures.

## 4.3    Send a Test Submission

After Test Account Setup and Transaction Partner approval, a test submission must be sent to ensure that the submission "conduit" is working properly from end to end. To do this, follow the steps below.

**Confirm that the correct version of the JRE is installed before you begin.  Reference** *Appendix D, Java Runtime Edition Installation* **for the version information and installation procedures.**

1.  Using the address provided by the FDA, access the FDA ESG Web Interface application. The **Login** page is displayed.



Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not send a test submission. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.gov to request access to the test environment.

2.  Enter the **User ID** and **Password** that was set up in the registration wizard. Reference Step 9 in *Section 4.1, Apply for a Test Account.*

3.   Click the **Login** button.

After a successful login, the **Documents in Inbox** page is displayed. The **Documents in Inbox** page lists all messages received from the FDA ESG.
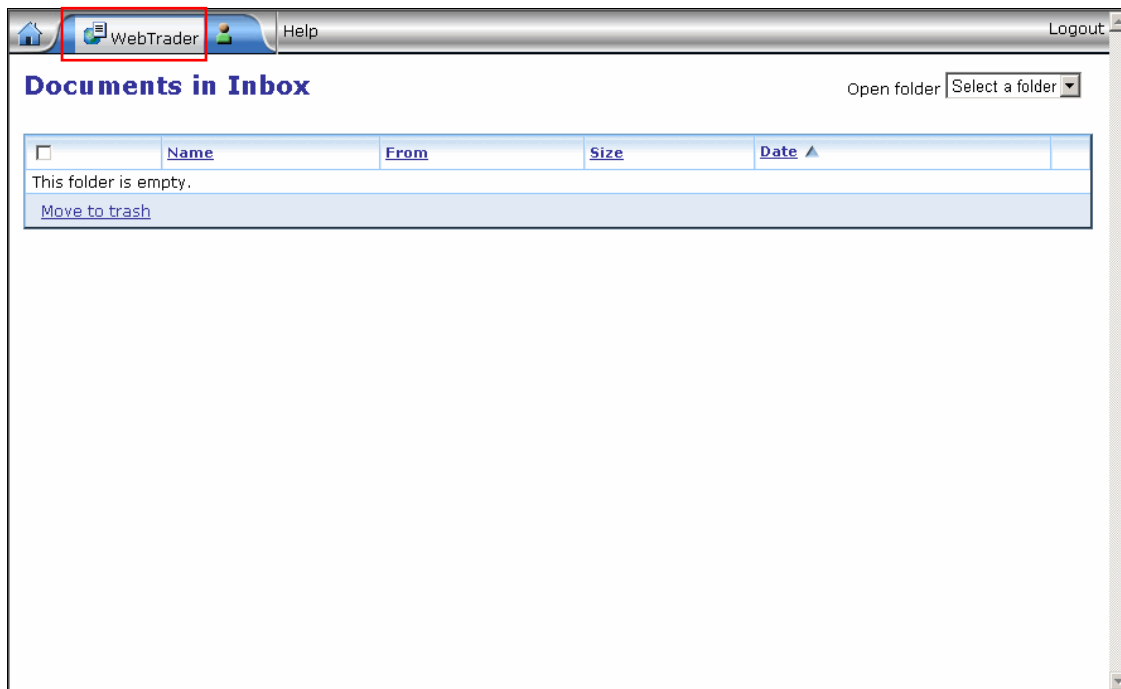
4.   Click the **WebTrader** icon.

   The **WebTrader** drop-down menu is displayed.
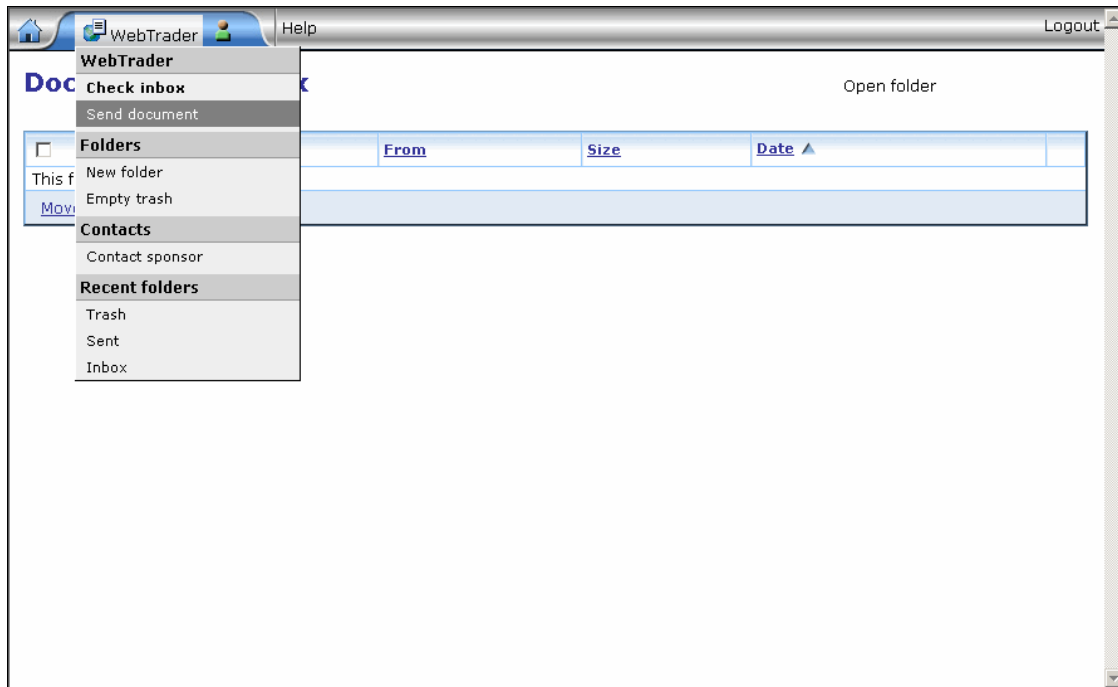


5.   Select the **Send document** menu item.

   A Security Warning window for the certificate is displayed.

6.   Select either **Yes** or **Always**. Selecting **Yes** makes this warning window appear each time the **Send document** menu item is used. Selecting **Always** ensures that this window is not displayed again on the current machine when the **Send document** menu item is used.

**NOTE: Selecting No on this window disables the options for some fields on this page, and prevents the progress of the process. If this option is mistakenly selected, use the browser's Back button to return to the previous page.**

A second Security Warning window is displayed.
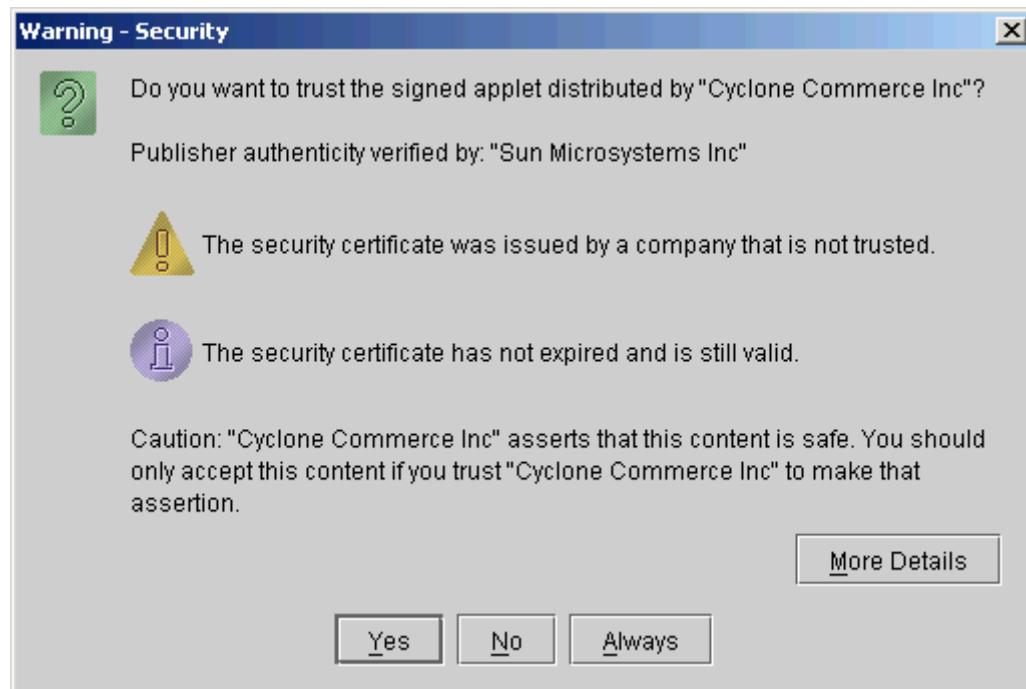


7.   Select either **Yes** or **Always**. Selecting **Yes** makes this warning window appear each time the **Send document** menu item is used. Selecting **Always** ensures that this window is not displayed again on the current machine when the **Send document** menu item is used.

**NOTE: Selecting No on this window disables the options for some fields on this page, and prevents the progress of the process. If this option is mistakenly selected, use the browser's Back button to return to the previous page.**

The **Send document** page is displayed.

8. Select an FDA Center from the **Center** drop-down box. The Centers that can be selected at present are CBER, CDER, or CDRH. Upon choosing a Center, the **Submission type** drop-down box will be populated with the correct submission types for that Center.

9. Single File Submissions: Click the **Browse** button associated with the **Path** textbox to select the test submission.

10. Multi-File Submissions: Click the **Browse** button associated with the **Root Directory** textbox to select the directory that contains all the files in the test submission.

11. Select a test submission type from the **Submission type** drop-down box.

12. Select a signing certificate by clicking the associated **Browse** button and selecting the signing certificate. All submissions require a certificate to digitally sign and encrypt the submission.

The completed **Send document** page should be populated similar to the page below.

13. Click the **Send** button on the **Send document** page.

The **Enter password** dialog box is displayed on top of the **Send document** page.

14. Enter the certificate password and click **OK** in this dialog box.

   The **Upload Progress** dialog box is displayed on the **Send document** page:
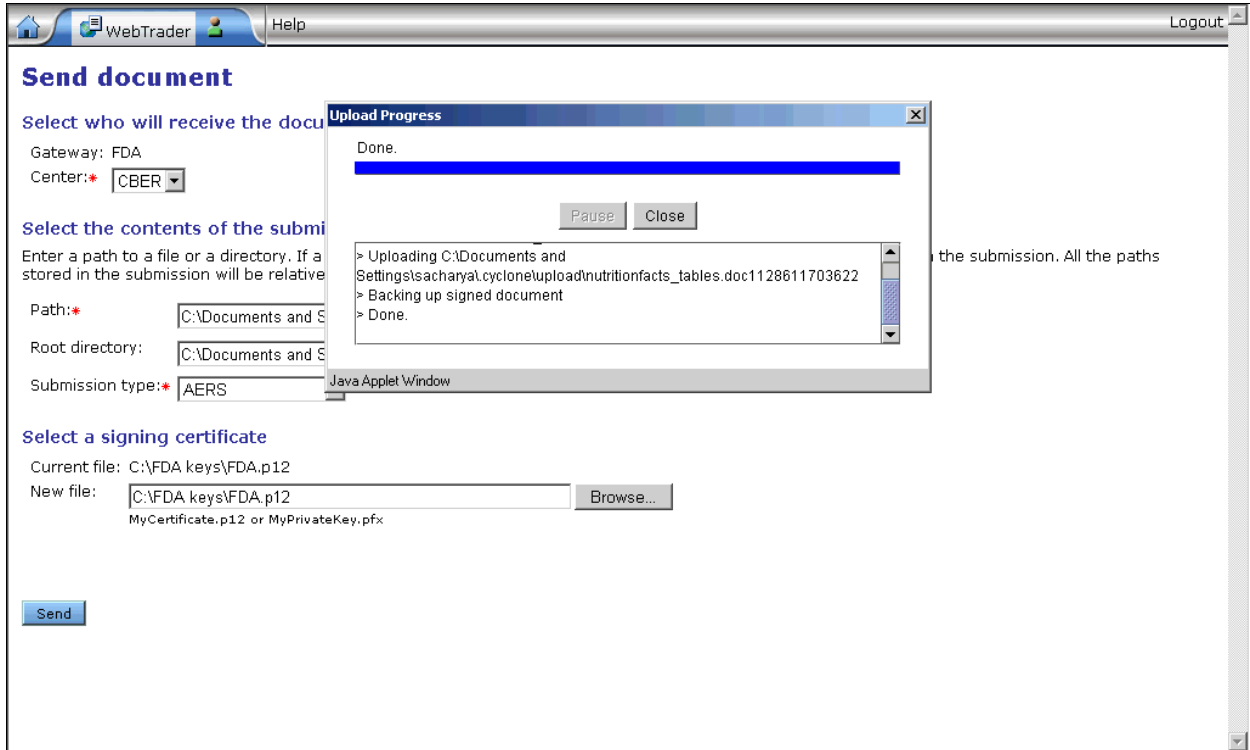


15. When the upload is complete (indicated by displaying **Done**), click the **Close** button in the **Upload Progress** dialog box.

   At this point, the test submission is sent. The FDA ESG logs the submission and verifies submission destination and type. When the submission is successfully received at the FDA, a receipt email will be listed on the **Documents in Inbox** page.

To access the receipt,

16. Click on the **WebTrader** icon to access the Inbox.

The **WebTrader** drop-down menu is displayed.

17. Select the **Check inbox** menu item.

The **Documents in Inbox** page is displayed.



The receipt for the test submission should be displayed here. This first receipt confirms that the submission was received by the FDA ESG. Click on the Details link to access the receipt contents.

If there are any errors in the submission, a notification is sent to the **Documents in Inbox** page.

The FDA ESG will then route the test submission to the Center Holding Area. When the Center system successfully receives the submission, a second acknowledgement will be sent confirming that the Center has received the submission. The Center will then validate the test submission. If the submission was valid, the Center will then send back a third Acknowledgement to the **Documents in Inbox** page.

Contact the FDA ESG testing representative at esgprep@fda.gov if the receipt for the test submission or the Center Acknowledgements are not received.

The next step is to apply for an FDA ESG Production System Account. This process is described in the following section.

## 4.4 Apply for a Production System Account

The steps for applying for an FDA ESG Production System Account are the same as those described in *Section 4.1, Apply for a Test Account.*

However, there is a difference in the Login page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown below:



If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.gov and obtain the correct address for the FDA ESG Login page.

## 4.5     Production System Account Setup and Approval

After successfully completing the Production System Account setup, the FDA sends an email to the email address provided for the primary contact, indicating approval as a Transaction Partner and authorization to send submissions to the FDA ESG. Typically, the approval notification is sent on the next business day.

Submissions cannot be sent to the FDA ESG until this notification has been received.

## 4.6     Send Submissions to the Production System

The steps to send a Submission to the FDA ESG are the same as those in *Section 4.3, Send a Test Submission.*

However, there is a difference in the Login page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown in *Section 4.4, Apply for a Production System Account*.

If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.gov, and obtain the correct address for the FDA ESG Login page.

## 4.7     Sending Large (> 7.5 GB) Submissions

The FDA ESG is able to receive and process regulatory submissions up to 100 GB in size.  The major consideration in determining how quickly large submissions are transmitted to the FDA ESG is the bandwidth available to the Transaction Partner between their company and the FDA ESG.  FDA has the following recommendations concerning the transmission of large regulatory submissions.

- During the testing phase, send a 7.5 GB test submission.  This test will allow Transaction Partners to evaluate bandwidth availability and to adjust their network configuration as necessary.

- Send a 7.5 GB test submission that is representative of an actual submission.  The web interface archives and compresses the submission into a single file prior to transmission. Submissions that consist of text files will compress to a greater extent than PDF files, will transmit faster, and thus give an inaccurate assessment of the time it takes for submissions to be sent and processed by the FDA ESG.

- Send submissions greater than 7.5 GB in size overnight.  Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG.  These companies had T3 network connections or better.  FDA recommends that large submissions be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

Sending large submissions may result in the FDA ESG web interface erroneously reporting that the transmission was not successful, even though the FDA ESG has successfully received the transmission.  This is a known bug and FDA has asked Cyclone Commerce to provide an update to the web interface that fixes this error.

When the FDA ESG has received a complete submission, a backup copy is made before the Java applet receives a reply from the server confirming the submission is complete.  For large

submissions (> 7.5 GB), this can take many minutes.  Since there is no network activity for such a long time, the session timeouts and the Java applet never receives the response.  The FDA ESG has received the submission successfully, but the Java applet returns an error and indicates that the submission needs to be resumed.  Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request.  Since this is a large submission, it will take several hours before the first acknowledgement is received.

If you receive this error and it has clearly occurred at the end of the transmission, do not resend the submission right away.  Wait for several hours (or longer depending on the size of the submissions) and see if the MDN is sent before attempting to resend the submission.

## 4.8     Tracking Submissions

Once a submission has been sent using the FDA ESG Web Interface, the Transaction Partner can track the submission to ensure that it was received by the FDA ESG and the Center.

### 4.8.1  The submission process

When a submission is sent using the FDA ESG Web Interface, it goes through the following steps:

1.  The submission is transmitted using the FDA ESG Web Interface to the Gateway. When the FDA ESG receives this submission, it sends a receipt known as a Message Delivery Notification (MDN) to the Inbox of the account from which the submission was received.
2.  The submission is delivered from the FDA ESG to a central holding area for all the Centers.
3.  The submission is then delivered from the holding area to the appropriate Center. When a Center receives a submission, it sends an acknowledgement to the Inbox of the account from which the submission was sent.

### 4.8.2  Message Delivery Notifications (MDNs) and acknowledgements

When a submission is sent using the FDA ESG web interface, the following two messages are delivered to the Inbox of the account from which the submission was sent.

1.  A receipt from the FDA ESG, also known as an MDN. This message denotes that the submission has been delivered to the FDA ESG. The name of the receipt message includes the file name of the submission that was sent.  If a directory of files was submitted, the file name of the submission will be the name of the directory followed by the extension ".tar.gz". The MDN message contains the message ID of the submission and a date stamp for when the submission was received by the FDA ESG. These items may be used to track a submission.
2.  An acknowledgement from the Center to which the submission was sent. This file is named with a unique alphanumeric string known as the Core ID. The Core ID is also used by the FDA ESG to track a submission.

A sample Inbox looks similar to this, once submissions have been sent:
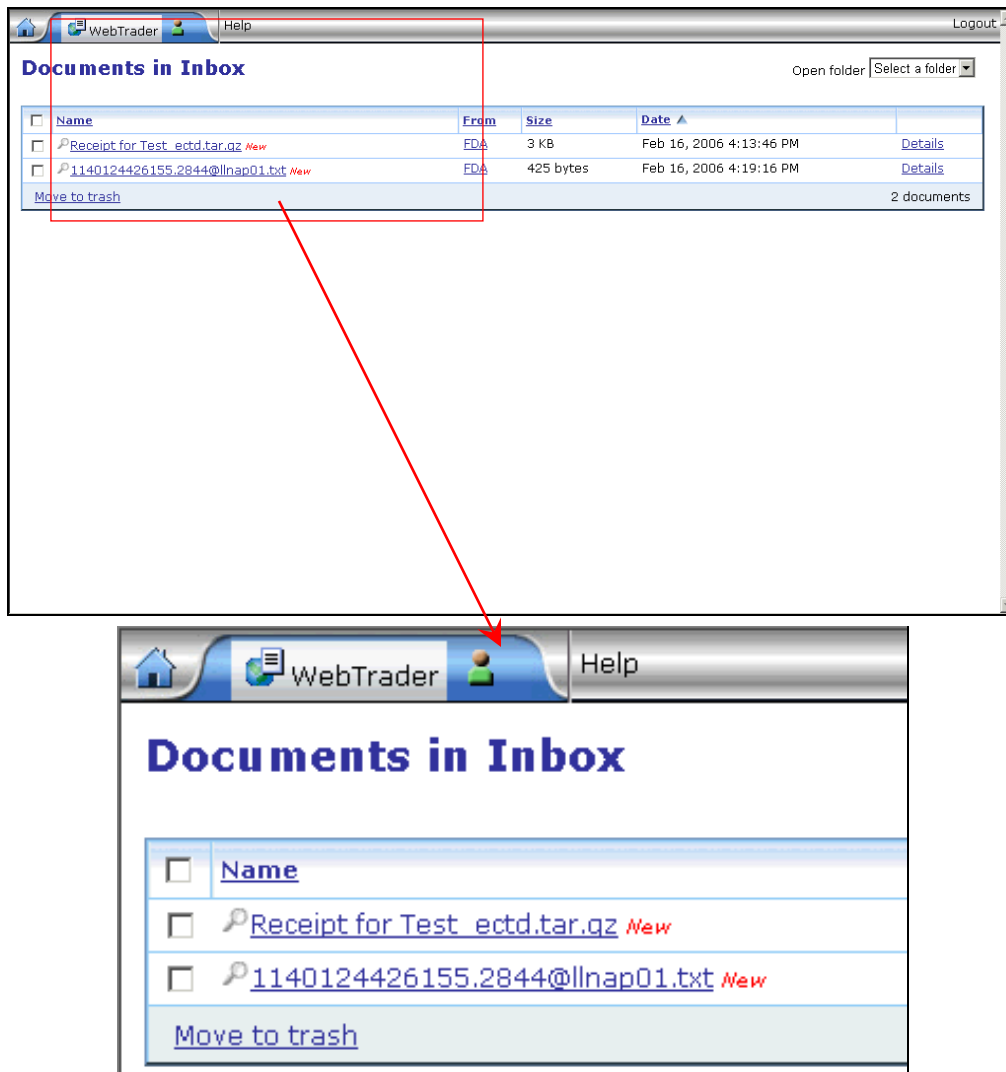
### 4.8.3  Message IDs and Core IDs

Among other information, the MDN contains a Message ID and a time stamp denoting the time the submission was received. The Message ID is a unique alphanumeric string that identifies each submission. This Message ID can be used to track a submission and to correlate a submission to its Center acknowledgement.

A sample MDN looks similar to the file shown below. The Message ID and date stamp in this
MDN are highlighted.

```
Message-ID: <1140124426654.2852@llnap01>
Date: Thu, 16 Feb 2006 21:13:46 GMT
From: esgprep@fda.gov
Subject: AcmeDrugCompany;ZZFDA
Mime-Version: 1.0
Content-Type: multipart/signed; micalg=sha1; protocol="application/pkcs7-
signature";  boundary="----=_Part_65_16583928.1140124426654"
X-Cyclone-From: ZZFDA
X-Cyclone-To: AcmeDrugCompany
Content-Length: 1952


------=_Part_65_16583928.1140124426654
Content-Type: multipart/report; report-type=disposition-notification;
        boundary="----=_Part_64_17446017.1140124426654"


------=_Part_64_17446017.1140124426654
Content-Type: text/plain; charset=us-ascii

This MDN (Message Disposition Notification) was automatically built on
Thu, 16 Feb 2006 21:13:46 GMT in response to a message with id
<12689343.1140124473009.JavaMail.sacharya@pvenkat> received from
ZZFDA on Thu, 16 Feb 2006 21:13:46 GMT.
Unless stated otherwise, the message to which this MDN applies
was successfully processed.

------=_Part_64_17446017.1140124426654
Content-Type: message/disposition-notification

Original-Message-ID: <12689343.1140124473009.JavaMail.sacharya@pvenkat>
Disposition: automatic-action/MDN-sent-automatically; processed
Received-Content-MIC: Jkm19bjOa6J8JBn/pv87oYIBnTA=, sha1
```

When a center receives a submission, it associates the submission's Message ID to a Core ID.
This Core ID can be used along with the Message ID generated as part of the MDN to track a
submission on the FDA ESG. A sample acknowledgement message with the Core ID highlighted
is shown below:

```
MessageId: <12689343.1140124473009.JavaMail.sacharya@pvenkat>


CoreId: 1140124426155.2844@llnap01


DateTime Receipt Generated: 02-16-2006, 16:17:11


The date and time stamp contained in this message conveys when CBER
received your submission from the Electronic Submission Gateway.  If
your submission was received at CBER after 4:30 PM EST, the official
receipt date for the submission is the next government business day.
```

### 4.8.4  Accessing MDNs and acknowledgements

To access an MDN after sending a submission,

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.
2. From the WebTrader menu, select the "Check inbox" option. The receipts that are displayed specify the name of the submission file as part of their name.
3. Click the Details link next to the name of the required receipt to see its details.

To access an acknowledgement after sending a submission,

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.
2. From the WebTrader menu, select the "Check inbox" option. The messages with ".ack" or ".txt" extensions are the acknowledgements from Centers for submissions. The message name before the extension denotes the Core ID generated by the Center for the submission.
3. Click on the name of the required acknowledgement to see its details.

### 4.8.5  Tracking a submission on the FDA ESG Web Interface

To track a submission on the ESG, you will need the following information about the submission:

- Core ID of the submission (generated by the FDA ESG and included as part of the acknowledgement)

- Message ID of the submission (captured by the FDA ESG and included as part of the MDN)

- Time stamp when the submission was received by the FDA ESG (generated by the FDA ESG and included as part of the MDN)

To gather this information, follow the steps given below once you have sent the submission and received both its MDN and acknowledgement.

1. Access the MDN of the submission using the procedure given in *Section 4.8.3 , Message IDs and Core IDs*. Locate the Message ID and time stamp and make a note of this information.
2. Access the acknowledgement using the procedure given in *Section 4.8.3 , Message IDs and Core IDs*. Locate both the Message ID and the Core ID in this file, and make a note of this information.
3. Compare the Message IDs in both files. For instance:

```
This MDN (Message Disposition
Notification) was automatically
built on
Thu, 16 Feb 2006 21:13:46 GMT in
response to a message with id
<12689343.1140124473009.JavaMail
.sacharya@pvenkat> received from
ZZFDA on Thu, 16 Feb 2006
21:13:46 GMT.
Unless stated otherwise, the
message to which this MDN
applies
was successfully processed.
```

```
MessageId:
<12689343.1140124473009.JavaMail
.sacharya@pvenkat>


CoreId:
1140124426155.2844@llnap01


DateTime Receipt Generated: 02-
16-2006, 16:17:11
```

4. If the Message IDs match (as is the case above), both the MDN and acknowledgement pertain to the same submission (the name of which is the name of the MDN receipt file).

# 5.  AS1 Gateway-to-Gateway Electronic Submissions

**NOTE: The AS1 protocol will only be used to send/receive AERS submissions. Other submission types (including AERS reports) can be sent using the FDA ESG Web Interface or the AS2 Gateway-to-Gateway protocol.**

Additionally:

- AS1 Gateway-to-Gateway submission can be only AERS and AERS Attachments intended for CBER or CDER.

- AERS reports may be in XML or EDI/SGML format, however; XML is the preferred format.

  For more information on preparing SGML submissions, go to:
  http://www.fda.gov/cder/aerssub/SGML.htm

- AERS attachments must be in PDF format.

  For more information on preparing PDF attachments, go to:
  http://www.fda.gov/cder/guidance/4153dft.pdf
  (specifically, Section III.B - which starts at line 243).

- All submissions must be signed electronically with a digital certificate.

**FDA ESG support for the AS1 protocol will be phased out by May 2007.**

The steps below represent the current understanding of the AS1 Gateway-to-Gateway submission process. Further refinement and clarification of these steps will be provided in future revisions of the user guide.

## 5.1    Apply for a Test Account

1. An online application form is provided for Transaction Partners to register for an AS1 test account. The registration web address and a temporary Login ID and password can be obtained from the FDA ESG Administrator by sending an email to esgprep@fda.gov indicating intent to register for the FDA ESG.

2. The following information is required to complete the AS1 application form.

- Contact information - The name and contact information of a person whom the FDA may contact for questions or additional information. Enter the following information:
  - Company name
  - Primary Contact name
  - Primary Contact phone
  - Primary Contact email
  - Alternate contact name
  - Alternate phone
  - Alternate email

**NOTE: Partners who have either an FDA ESG or AS2 account already, must enter a unique string (different from the one used when registering for the FDA ESG or AS2 account) in the Company name field. This is to ensure that this account is treated as a separate identity in the database.**

- The email address from where test submissions will be sent and where acknowledgements and notifications will be received from the FDA.

- The digital certificate used to digitally sign and encrypt the test submission.

- The organization's ID number. This could be, but does not have to be the Data Universal Numbering System (DUNS) number.

## 5.2    Test Account Setup and Approval

After submitting the application information as described above, the FDA ESG Administrator will communicate with the Primary Contact to validate the information provided, setup the test account, and test the AS1 Gateway-to-Gateway connection.

The FDA ESG Administrator will provide the following information so that the Transaction Partner can set up an account for the FDA ESG within their Gateway. This FDA ESG account will enable the receipt of messages from the FDA ESG.

- The FDA test contact information [the FDA's Office of Chief Information Officer (OCIO) testing representative ]

- The email address at which the FDA will want to receive test submissions and send messages back to the Transaction Partner

- The FDA digital certificate for test submissions

- The FDA ID number

At this point the Gateway-to-Gateway connection will be tested to ensure that secure emails from the Transaction Partner to the FDA ESG and from the FDA ESG to the Transaction Partner's AS1 Gateway are successfully received.

## 5.3    Send a Test Submission

1. Contact the FDA's OCIO testing representative at [esgprep@fda.gov](mailto:esgprep@fda.gov) to schedule a specific test date and time.
2. At the scheduled date and time, send the test submission to the FDA.

   The FDA ESG will send an MDN indicating that the test submission was received successfully.

   The FDA ESG will then route the test submission to the AERS Holding Area.  AERS will validate the test submission.

   At Center/programmatic area option an Acknowledgement can be sent (via AS1) indicating whether the submission was valid or invalid.

3. Contact the FDA's OCIO testing representative if the AERS Acknowledgement or the MDN is not received.

Once a test submission has been successfully received and validated (this normally takes more than one test submission), the Transaction Partner is approved to apply for and setup a Production System Account. This account will be used to send AERS reports to the FDA.

## 5.4    Apply for a Production System Account

The steps for applying for a Production System AS1 Gateway Account are the same as those described in *Section 5.1, Apply for a Test Account*.

## 5.5    Production System Account Setup and Approval

The steps for setup and approval of a Production System AS1 Gateway Account are the same as those described in *Section 5.2, Test Account Setup and Approval*. Upon completion of this step, the Transaction Partner is now ready to send AERS reports to the FDA ESG.

## 5.6    Send Submissions to the Production System

For each AERS report sent to the FDA ESG, two messages will be sent back to the Transaction Partner.

1.  The Transaction Partner will receive the MDN from the FDA ESG indicating that the submission was received successfully.
2.  Indication of submission validity or invalidity (at Center/programmatic area option).

# 6.  AS2 Gateway-to-Gateway Electronic Submissions

The steps below represent the current understanding of the AS2 Gateway-to-Gateway submission process. Further refinement and clarification of these steps will be provided in future revisions of the user guide.

## 6.1    Apply for a Test Account

1.  An online application form is provided for Transaction Partners to register for an AS2 test account. The registration web address and a temporary Login ID and password can be obtained from the FDA ESG Administrator by sending an email to esgprep@fda.gov indicating intent to register for the FDA ESG.

2.  The following information is required to complete the AS2 application form.

- Contact information - The name and contact information of a person whom the FDA may contact for questions or additional information. Enter the following information:

    - Company name

    - Primary Contact name

    - Primary Contact phone

    - Primary Contact email

    - Alternate contact name

    - Alternate phone

    - Alternate email

**NOTE: Partners who have either an FDA ESG or AS1 account already, must enter a unique string (different from the one used when registering for the FDA ESG or AS1 account) in the Company name field. This is to ensure that this account is treated as a separate identity in the database.**

- The Website address from where test submissions will be sent and where acknowledgements and notifications will be received from the FDA.

- The digital certificate used to digitally sign and encrypt the test submission.

- The organization's ID number. This could be, but does not have to be the Data Universal Numbering System (DUNS) number.

- Firewall security information:

    - Secure Socket Layer (SSL) Information – user name and password (if one is needed for SSL)

    - Proxy Information – if a proxy server is used.

## 6.2    Test Account Setup and Approval

After submitting the application information as described above, the FDA ESG Administrator will communicate with the Primary Contact to validate the information provided, to setup the test account, and to test the AS2 Gateway-to-Gateway connection. At that time, the FDA ESG Administrator will also obtain security and proxy information from the Transaction Partner.

The FDA ESG Administrator will provide the following information so that the Transaction Partner can set up an account for the FDA ESG within their own Gateway. This FDA ESG account will enable the receipt of messages from the FDA ESG.

- The FDA ESG Administrator's contact information
- The Website address at which the FDA will want to receive the test submissions
- The FDA digital certificate for test submissions
- The FDA ID number

At this point the Gateway-to-Gateway connection will be tested to ensure that secure messages from the Transaction Partner to the FDA ESG and from the FDA ESG to the Transaction Partner's AS2 Gateway are successfully received.

## 6.3    Send a Test Submission

1. Contact the appropriate Center testing representative to schedule a specific test date and time. Reference *Section 3.3, Understand Submission Guidelines* for information on how to prepare an electronic submission and Center contact information.

2. For multi-file submission, the entire submission must reside in a single directory. This directory must then be converted to a single .tar.gz file. Reference *Appendix B, Creating tar Files and Compressing Files for Submission,* for instructions on creating this compressed file.

3. Add information to the header of the file to indicate the type of submission (e.g., an IND) and destination (e.g., CBER). Reference *Appendix G, AS2 Header Attributes,* for information on header attribute content and format.

4. At the scheduled date and time, send the test submission to the FDA.

   The FDA ESG will send an Mail Delivery Notification (MDN) indicating that the test submission was received successfully.

   The FDA ESG will then route the test submission to the Center Holding Area.  The Center will validate the test submission.  For submissions other than AERS reports, an Acknowledgement will be sent documenting the official date and time of retrieval from the Center Holding Area and Center/programmatic area business rules describing the establishment of that date and time.

   The Centers/programmatic area has the option to send an Acknowledgement (via AS2) indicating whether the submission was valid or invalid.

5.  Contact the appropriate Center testing representative if the Center Acknowledgement is not received. Contact the FDA ESG Administrator at <u>esgprep@fda.gov</u> if the MDN is not received.

Once a test submission has been successfully received and validated, the Transaction Partner is approved to apply for and setup a Production System Account. This account will be used to send submissions to the FDA.

## 6.4    Apply for a Production System Account

The steps for applying for a Production System AS2 Gateway Account are the same as those described in *Section 6.1, Apply for a Test Account*.

Be sure to indicate on the application form that this application is for a Production System Account.

## 6.5    Production System Account Setup and Approval

The steps for setup and approval of a Production System AS2 Gateway Account are the same as those described in *Section 6.2,*

*Test Account Setup and Approval.* Upon completion of this step, the Transaction Partner is now ready to send submissions to the FDA ESG.

## 6.6    Send Submissions to the Production System

For each submission sent to the FDA ESG, at least two messages will be sent, and up to three messages will be sent back to the Transaction Partner.

1. The Transaction Partner will receive the MDN from the FDA ESG indicating that the submission was received successfully.

2. For submissions other than AERS reports, an Acknowledgement will be sent that the submission was retrieved from the Center Holding area. This Acknowledgement will contain the official date and time of retrieval and Center/programmatic area business rules describing the establishment of that date and time.

3. Indication of submission validity or invalidity (at Center/programmatic area option).

## 6.7    Sending Large (> 7.5 GB) Submissions

The FDA ESG is able to receive and process regulatory submissions up to 100 GB in size.  The major consideration in determining how quickly large submissions are transmitted to the FDA ESG is the bandwidth available to the Transaction Partner between their company and the FDA ESG.  FDA has the following recommendations concerning the transmission of large regulatory submissions.

- During the testing phase, send a 7.5 GB test submission.  This test will allow Transaction Partners to evaluate bandwidth availability and to adjust their network configuration as necessary.

- Send a 7.5 GB test submission that is representative of an actual submission.  The web interface archives and compresses the submission into a single file prior to transmission.  Submissions that consist of text files will compress to a greater extent than PDF files, will transmit faster, and thus give an inaccurate assessment of the time it takes for submissions to be sent and processed by the FDA ESG.

- Send submissions greater than 7.5 GB in size overnight.  Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG.  These companies had T3 network connections or better.  FDA recommends that large submissions be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

Sending large submissions may result in the FDA ESG erroneously reporting that the transmission was not successful, even though the FDA ESG has successfully received the transmission.  This is a known bug and FDA has asked Cyclone Commerce to provide an update to that fixes this error.

When the FDA ESG has received a complete submission, a backup copy is made before a reply from the FDA ESG is sent confirming the submission is complete.  For large submissions (> 7.5 GB), this can take many minutes.  Since there is no network activity for such a long time, the session timeouts and a response is not received.  The FDA ESG has received the submission successfully, but an error is generated indicating that the submission needs to be resumed.  Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request.  Since this is a large submission, it will take several hours before the first acknowledgement is received.

If you receive this error and it has clearly occurred at the end of the transmission, do not resend the submission right away.  Wait for several hours (or longer depending on the size of the submissions) and see if the MDN is sent before attempting to resend the submission.

# 7. References/Resources

The following table provides some additional references and resources related to electronic submissions and the FDA ESG.

**Table 7-1: Additional References**

| Document | Web Link |
|---|---|
| CBER Annual Report FY 2002 | http://www.fda.gov/cber/inside/annrpt.htm#toc |
| CVM Electronic Submissions Project | http://www.fda.gov/cvm/index/esubs/esubstoc.html |
| Docket 92S-0251: Electronic Submissions | http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm |
| Electronic Regulatory Submissions and Review | http://www.fda.gov/cder/regulatory/ersr/default.htm |
| Electronic Submissions through the FDA ESTRI GATEWAY Frequently Asked Questions (FAQ) | http://www.fda.gov/oc/electronicsubmissions/interfaq.htm |
| FDA AERS Electronic Submissions Web Site | http://www.fda.gov/cder/aerssub/default.htm |
| Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application | http://www.fda.gov/cder/guidance/5667fnl.htm |
| Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs and ANDAs | http://www.fda.gov/cber/gdlns/esubnda.pdf |
| Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Postmarketing Expedited Safety Reports | http://www.fda.gov/cder/guidance/4153dft.pdf |
| Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format - Investigational New Drug Applications (INDs) | http://www.fda.gov/cber/gdlns/eind.pdf |
| Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations | http://www.fda.gov/cder/guidance/2867fnl.pdf |
| Guidance for Industry: Providing Regulatory Submissions to Office of Food Additive Safety in Electronic Format -- General Considerations | http://vm.cfsan.fda.gov/~dms/opaeguid.html |
| ICH Home Page | http://www.ich.org/ |
| PDUFA Main Page on FDA Site | http://www.fda.gov/oc/pdufa/default.htm |
| PhRMA Home Page | http://www.phrma.org/ |
| CDER AERS Electronic Submissions Pilot Web Site | http://www.fda.gov/cder/present/dia-299/yaplee/ |

## APPENDIX A.  Troubleshooting the FDA ESG Web Interface

**Problem**: Started sending wrong submission

**Solution**: When the upload progress window appears, press **Cancel** and this will cease the uploading of that submission.

---

**Problem**: Computer froze/crashed while sending the file.

**Solution**: If the submission had begun transmitting (i.e., signing was already completed) to the FDA ESG when the computer froze or crashed, log back into the FDA ESG web interface. The file you were attempting to send will be on the top left hand side. Your options are to resume sending or deleting the submission. Check to make sure there is ample disk space. It is recommended that you have disc space of at least three times the size of the transmission.

---

**Problem**: Received a disk space error.

**Solution**: Make sure there is ample disk space to backup the submission. It is recommended that you have disk space of at least three times the size of the transmission. Note that every time a submission is sent to the FDA ESG, a back up copy of the packaged (encrypted, tarred, and gzipped) submission file is stored on the local PC. This backup file is stored under:

C:\Documents and Settings\<your identity>\.cyclone\backup.

These backup copies can be deleted by first logging in to the FDA ESG web interface. Then go to: WebTrader➔Recent Folder➔Sent.

Select the desired entries for deletion. This will remove entries from the Sent view and will also remove the backup files from the backup directory on the local PC.

---

**Problem**: Received a signing encryption error

**Solution**: Verify the correct public key certificate was uploaded during the registration process by contacting the FDA ESG Administrator at esgprep@fda.gov and comparing the md5 fingerprints within the certificate.

---

**Problem**: Received a private key error

**Solution**: This error occurs when there is a mismatch between the public and private key for a certificate. Check to ensure the correct private key for the public certificate sent to the FDA ESG is in place. Obtain the correct private key and resend the document.

---

**Problem**: A FIPS error was received while sending a submission

**Solution**: Make sure the correct JRE version or security policies are properly installed. Reinstall the JRE using instructions provided with that package. Reference *Appendix D,*

*Java Runtime Edition* Installation for more information.

---

**Problem**: The following error was received when trying to import a digital certificate using the FDA ESG Web interface:

"Invalid certificate file

An error has occurred while importing the certificate file. Most likely you selected the wrong file type."

**Solution**: 1) Check the file extension. The file extension must be ".p7b" or ".cer". Files with these extensions represent the public key part of the certificate. Only the public key part of the certificate can be imported. Reference *Appendix C*,

*Digital* Certificates for more information. 2) Make sure the local PC has been configured to recognize and use the digital certificate. Reference the operating system instructions on the local PC for more information.

---

**Problem**:  When using the FDA ESG Web interface, an error message was received at the very end of a submission saying there was no response from the server and that the submission failed.

**Solution**:  When the FDA ESG has received a complete submission, a backup copy is made before the Java applet receives a reply from the server confirming the submission is complete. For large submissions (> 7.5 GB), this can take many minutes.  Since there is no network activity for such a long time, the session timeouts and the Java applet never receives the response.  The FDA ESG has received the submission successfully, but the Java applet returns an error and indicates that the submission needs to be resumed.  Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request.  Since this is a large submission, it will take several hours before the first acknowledgement is received.

FDA has asked Cyclone Commerce to provide an update to the web interface that fixes this error.

## APPENDIX B.  Creating tar Files and Compressing Files for Submission

### Creating tar files for FDA ESG Web Interface Submissions

During the file upload process, the FDA ESG Web Interface utilizes the tar functionality for file system consolidation when submitting files. The process occurs during the electronic "signing" of the submission. Before the file is transmitted, it is tarred and gzipped, encrypted, signed, and mime-wrapped (or packaged) before transmitting to the FDA ESG.

The figure below illustrates this process.



**Industry**

**Gateway acknowledgement**

Multifile or directory
submission,
eIND demos

eIND

**FDA ESG**

File is tarred and gzipped,
then encrypted/mime wrapped

Upon receiving the file,
signature is verified, file
is unzipped/untarred,
unwrapped/decrypted,
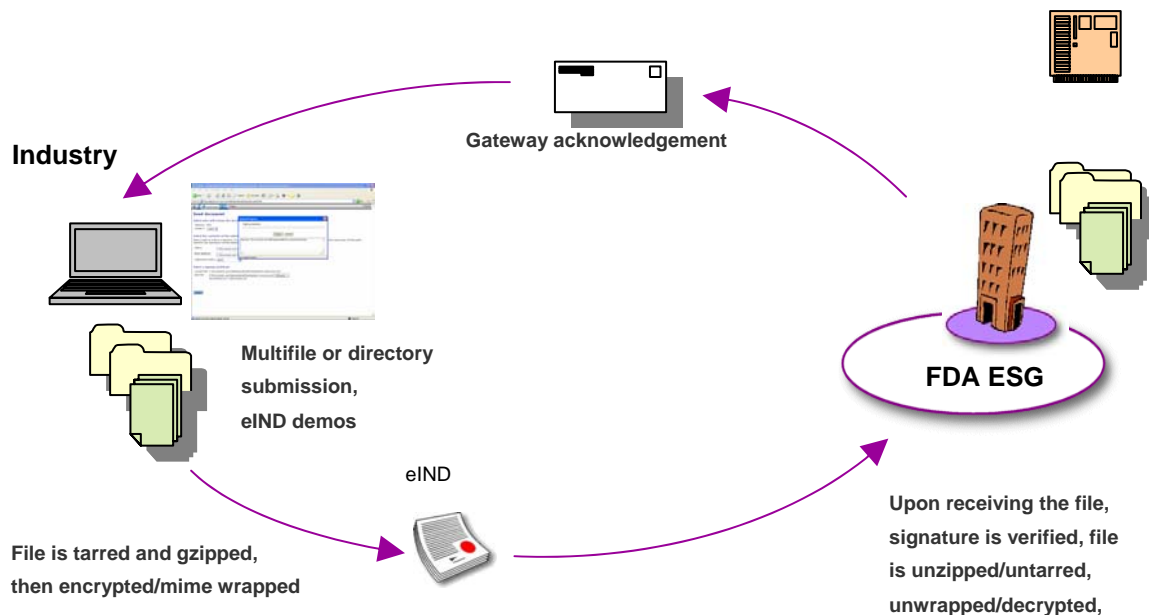
Because this process is done automatically during the signing of the file, no intervention is required from the user to ensure the file is tarred and gzipped.

### Creating tar files for Gateway-to-Gateway Submissions

Partners are required to both tar and gzip (compress) multifile submissions. (gzip is the original UNIX ZIP format and is used as a compression utility to reduce the size of the archive file.)

For best optimization when processing and transmitting large submission files, first "tar" the files and then compress them using gzip. Valid files acquire a .tar.gz extension resulting from the process of tarring the directory (containing multiple files) and gzipping the created tar archive.

The figure below illustrates this process.



**Gateway acknowledgement**

eIND

**FDA ESG**

eIND

**Gateway to Gateway
must use extension .tar.gz**

**Upon receiving the file,
signature is verified, file
is unzipped/untarred,
unwrapped/decrypted,**
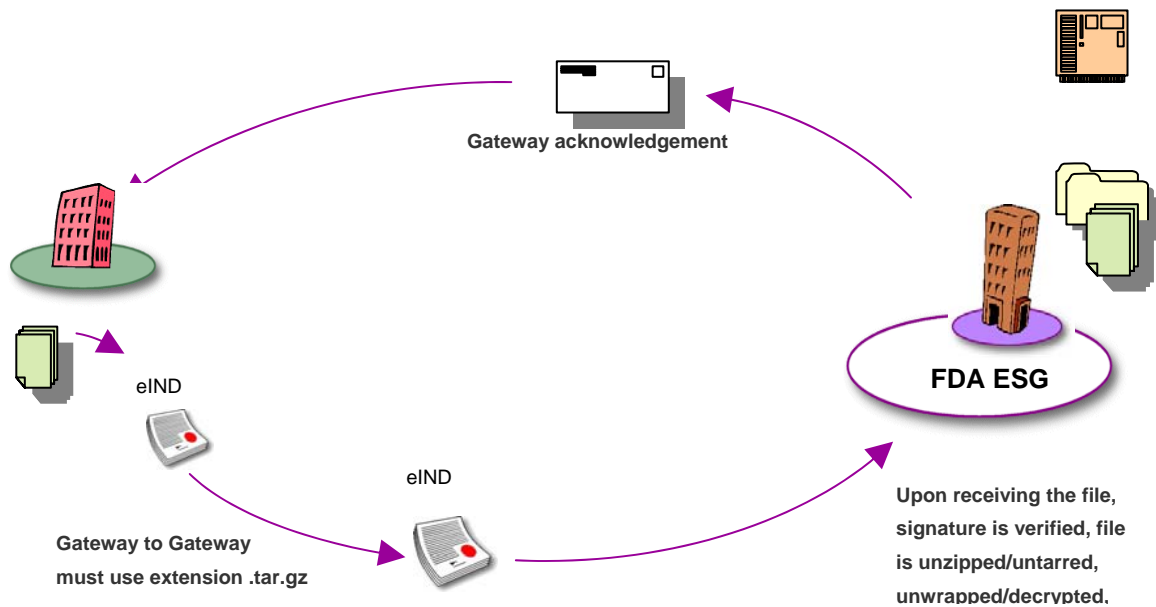
To fulfill this requirement, the current AS1/AS2 solution will/should have a tar and zip utility prescribed. There are Operating System-specific utilities available for performing the tar operation.

If the application does not have tar/gzip capabilities, a utility must be acquired. Listed below are recommended utilities that support tar and gzip manually (external from application) or automatically (to be integrated with application).

- To create tar files: GNU Tar Utility at http://www.gnu.org/software/tar/tar.html

- To gzip files: gzip Utility at http://www.gzip.org/

Apache Ant Java package should be integrated into the application when creating .tar.gz files automatically through the application.

# APPENDIX C.    Digital Certificates

A digital certificate is an electronic document which conforms to the International Telecommunications Union's X.509 specification. It is a document which typically contains the owner's name and public key, the expiration date of the public key, the serial number of the certificate, and the name and digital signature of the organization which issued the certificate. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

Encrypting and digitally signing documents using certificates provides the following assurances about document transmissions:

- Only the addressee (and no unauthorized users) can read the message. Encryption provides this assurance.

- The message cannot be tampered with. That is, data cannot be changed, added, or deleted without the sender's knowledge. A document's digital signature provides this assurance.

- Parties sending documents are genuinely who they claim to be. Likewise, when those parties receive documents signed by the sender, they can be confident about the source of the documents. A document's digital signature provides this assurance.

- The parties who send documents cannot readily claim they did not send them. This is referred to as non-repudiation of origin. A document's digital signature provides this assurance.

- Parties who are sent documents cannot readily claim they did not receive them. This is referred to as non-repudiation of receipt. The signed document acknowledgment provides this assurance.

**Using the certification**

The public key in the FDA's certificate is used to encrypt a document for transmission. The FDA ESG uses the public key to verify the digital signature of a document received from a specified source.

Before encrypted and signed documents (sent submissions) are exchanged with the FDA ESG, there must be a certificate exchange to obtain the other's certificate and public key. Each party obtains a certificate with a public-private key pair, either by generating a self-signed certificate or by obtaining a certificate from a Certificate Authority. The private half of the key pair always remains on the party's computer. The public half is provided to the FDA ESG during the registration process and includes the certificate and public key, or the certificate alone.

**Certificates not accepted by the registration module**

There are situations when a valid certificate is not accepted by the registration module and is identified as invalid. If this occurs, zip the certificate file and email it to the FDA ESG administrator at **esgprep@fda.gov**. Once received, FDA will assess the certificate and send a response.

**Certificates not accepted by the FDA ESG**

The FDA ESG cannot accept certificates with blank data elements in the Issuer or Subject fields. These certificates will cause the FDA ESG to fail due to a defect in the Gateway software.

## DO NOT SUBMIT CERTIFICATES WITH BLANK DATA FIELDS IN THE ISSUER AND SUBJECT FIELDS

**Where to obtain a certificate**

The FDA ESG supports Public Key Infrastructure (PKI) to securely trade submissions over the Internet. PKI is a system of components that use digital certificates and public key cryptography to secure transactions and communications.

PKI uses certificates issued by certificate authorities (CAs) to provide authentication, confidentiality, integrity and non-repudiation of data.

**Options**

There are two PKI options supported–commercial in-house, and outsourced PKIs. The option chosen can depend on a number of factors, such as cost, human and system resources, and the degree or sophistication of security desired. PKI establishes digital identities that can be trusted. The CA is the party in a PKI that is responsible for certifying identities. In addition to generating a certificate, this entails verifying the identity of a subscriber according to established policies and procedures. This is the case for in-house and outsourced PKIs.

In an organization that generates and uses its own self-signed certificates, the trading parties must verify the certificates and establish a direct trust. Once established that an identity or issuer of an identity can be trusted, the trust anchor's certificate is stored in a local trust list. The FDA ESG has a local trust list for storing and managing established trust relationships. The application maintains a list of common public CA certificates similar to those kept in web browsers. Although convenient, this predetermination of trust might not complement every organization's security policy. The decision of who to trust rests with the individual organization.

**In-House**

An in-house PKI makes it possible to achieve complete control of security policies and procedures. It also carries the burden of management and cost to set up and maintain the system.

**Outsourced**

Third-party certificate authorities can be leveraged to purchase keys and X.509 certificates for general use in trading and let the CA manage security policies and details such as certificate revocation. The level of outsourcing can range from purchasing an end-entity public key certificate of a certain validity period from a commercial PKI to outsourcing all of the PKI services that the organization requires.

## APPENDIX D.    Java Runtime Edition Installation

In order to connect and upload/send files successfully to the FDA via the FDA ESG Web Interface, you must obtain and install Sun's JRE 1.4.2_08 plug-in files for the browser. JRE security policy files must also be updated.

These two components can be retrieved from the following Java Sun site:

Client-side JRE.

The 1.4.2 JRE is available at the following Website address:

http://java.sun.com/products/archive/index.html.

Select "1.4.2_08" from the "J2SDK/J2RE - 1.4" drop-down menu to download the JRE.  Once you have been reviewed, proceed with the downloading of the JRE. Be sure to follow the wizard instructions.

**JRE Security Policy Files**

Clients must also install the Java Cryptography Extension (JCE) Unlimited Strength Jurisdiction Policy files in the browser's JRE. These files can be downloaded (in a zipped file) from the following Website address:

http://java.sun.com/j2se/1.4.2/download.html

These files will replace the existing files located in JRE's lib/security directory.

For example, Windows users would most likely put these files in C:\Program Files\Java\j2re1.4.2_08\lib\security. It is recommended that a copy of the existing JCE Limited Strength Jurisdiction Policy files is saved before replacing them. A copy of the entire security directory may be saved or the existing local_policy.jar and US_export_policy.jar may be renamed. These are the two main policy files updated in this process.

Once a copy is saved, proceed by unzipping and extracting the new files in the zip into the C:\Program Files\Java\j2re1.4.2_08\lib\security directory. These files should be copied directly into the lib\security directory. Be sure there are no other directories within this folder during the unzip process.

**Turning Off Automatic Updates**

The installed JRE will periodically prompt users to download the latest updates.  The most recent versions of the JRE (JRE 1.4.2_09 and JRE 1.5) will not work with the FDA ESG web interface and must NOT be downloaded and installed.  Automatic checking for updates can be disabled on the Windows operating system as follows:

- Select "Control Panel" from the "Start" menu.
- Double-click on the "Java" icon in the "Control Panel" window to launch the JRE control panel.
- Click on the "Update" tab.  There will be a checkbox labeled "Check for Updates Automatically".  Make sure the checkbox is not checked and then "Apply" the change.

## APPENDIX E.    Glossary of Terms

**Table E-1: Glossary of Terms**

| Term | Definition |
|---|---|
| AS1 | Applicability Statement 1. An electronic submission protocol that uses secure email for communications. |
| AS2 | Applicability Statement 2. An electronic submission protocol that uses HTTP/HTTPS for communications. |
| Certificate Authentication | Verification of the identity of a person or process. Authentication confirms that a message truly came from the source that sent it. |
| Certificate Authority (CA) | An organization that issues digital certificates containing the applicant's public key and other identification information. |
| Certificate Confidentiality | Assurance that a message has been disclosed only to the parties authorized to share the information. |
| Certificate Integrity | Assurance that the information has not been altered in any way and is precisely true to the source. |
| Community | An entity that contains all the necessary components for submission: a component that receives and routes submissions (the FDA ESG), and its external (e.g., a member of the regulated industry) and internal (e.g., FDA Center) Transaction Partners. |
| Digital Certificate | An attachment to an electronic message that allows the recipient to authenticate the identity of the sender via third party verification from an independent certificate authority. Digital certificates are used to identify encryption and decryption codes between message senders and recipients. |
| Non-repudiation | A means to provide proof of the integrity and origin of data, both in an non-forgeable relationship that can be verified by any third party at any time, or, an authentication that, with high assurance can be asserted to be genuine.<br><br>The sender of data is provided with proof of delivery and the recipient is assured of the sender's identity, so that neither can later deny having processed the data. |
| Private Key | In secure communication, an algorithmic pattern used to encrypt messages that only the corresponding public key can decrypt. The private key is also used to decrypt messages that were encrypted by the corresponding public key. The private key is kept on the user's system and is protected by a password.<br><br>The private key is normally known only to the key owner. Messages are encrypted using the public key (see below) and decrypted using the private key. For digital signatures, however, a document is signed with a private key and authenticated with the corresponding public key. |

| Term | Definition |
|------|------------|
| Public Key | The public key of a public-private key encryption. This key is used to confirm electronic signatures on incoming messages or to encrypt a message so that only the holder of the private key can decrypt the file or message. |
|  | A public key is held in a digital certificate. Public keys are usually published in a directory. Any public key can encrypt information; however, data encrypted with a specific public key can only be decrypted by the corresponding private key, which the key owner keeps secret. |
| Transaction Partner | The entity sending submissions/communicating with the receiving and routing component (the FDA ESG) of the community. |

## APPENDIX F.    Acronyms

A list of acronyms relevant to the FDA ESG is provided below:

**Table F-1: List of Acronyms**

| Acronym | Phrase |
|---------|--------|
| AERS | Adverse Event Reporting System |
| AS1 | Applicability Statement 1 |
| AS2 | Applicability Statement 2 |
| CA | Certificate Authority |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CFR | Code of Federal Regulations |
| DUNS | Data Universal Numbering System |
| eANDA | Electronic Abbreviated New Drug Application |
| eBLA | Electronic Biological License Applications |
| eCTD | Electronic Common Technical Document |
| eDMF | Electronic Drug Master File |
| eIDE | Electronic Investigational Device Exemption |
| eIND | Electronic Investigational New Drug Application |
| eNDA | Electronic New Drug Application |
| EDR | Electronic Document Room |
| FDA | Food and Drug Administration |
| FDA ESG | FDA Electronic Submissions Gateway |
| HTTP | Hyper Text Transfer Protocol |
| HTTPS | Hyper Text Transfer Protocol Secure |
| IND | Investigational New Drug |
| JCE | Java Cryptography Extension |
| JRE | Java Runtime Edition |
| MDN | Message Delivery Notification |

| Acronym | Phrase |
|---------|--------|
| OCIO | Office of Chief Information Officier |
| PDUFA | Prescription Drug User Fee Act |
| PKI | Public Key Infrastructure |
| RAM | Random Access Memory |
| SSL | Secure Socket Layer |

## APPENDIX G.    AS2 Header Attributes

In addition to tarring/gzipping the actual documents, AS2 submissions must include the following attributes in their AS2 headers. The additional information is comprised of:

> FDA submissions Type
> FdaSubmissionType: Abbreviated New Drug (add submission type information)

> Center Name
> FdaCenter: CDER (add Center information)

The Mime Headers are to be located in the outermost MIME wrapper and will appear as follows:

X-Cyclone-Metadata-FdaSubmissionType: Abbreviated New Drug
X-Cyclone-Metadata-FdaCenter: CDER

The following example represents how the standard AS2 mime header should appear after appending the Center and SubmissionType attributes and upon and presented at the FDA ESG.

> Message-ID: <1115406057162.328983@WIN2K3-ESX6>
> Date: Fri, 06 May 2005 19:00:57 GMT
> From: esx6
> Mime-Version: 1.0
> Content-Type: application/pkcs7-mime; smime-type=enveloped-data;
> name=smime.p7m
> Content-Transfer-Encoding: binary
> Content-Disposition: attachment; filename=smime.p7m
> Disposition-Notification-To: esx6
> Disposition-Notification-Options: signed-receipt-protocol=optional,
> pkcs7-signature; signed-receipt-micalg=optional, sha1
> AS2-Version: 1.1
> AS2-To: db-as2
> AS2-From: esx6-as2
> **X-Cyclone-Metadata-FdaSubmissionType: EANDA**
> **X-Cyclone-Metadata-FdaCenter: CDER**
> Content-Length: 3607

This information must be included in the outermost portion of the outermost MIME wrapper.

The table below indicates the allowable attribute values for each FDA Center destination:

**Table G-1: Allowable Center Attribute Values**

| Center Destination | Allowed Attribute Values |
|---|---|
| CBER | AERS<br>AERS Attachments<br>EBLA<br>ECTD<br>EIDE<br>EIND<br>eDMF |
| CDER | AERS<br>AERS Attachments<br>EANDA<br>EBLA<br>ECTD<br>ENDA<br>EIND |
| CDRH | Adverse Events<br>Electronic Submissions |

## APPENDIX H.    Sample Letters of Non-Repudiation Agreement

A letter of Non-Repudiation Agreement for digital signatures must be submitted to the FDA prior to registering as a transaction partner for the FDA ESG. The letter must be submitted in paper form (preferably on company letterhead) and signed with a traditional handwritten signature. The letter must be sent to:

>   Office of Regional Operations (HFC-100)
>
>   5600 Fishers Lane
>
>   Rockville, MD 20857.

A copy must be sent to:

>   Michael Fauntleroy
>
>   Office of the Director (HFM-25)
>
>   Center for Biologics Evaluation and Research
>
>   Food and Drug Administration
>
>   11400 Rockville Pike, Room 4119
>
>   Rockville, MD 20857.

The following two letters are provided as samples for a Letter of Non-Repudiation Agreement. The information in square brackets [] will be provided by the submitter.

**SAMPLE LETTER #1**

[Company Letterhead]

[Today's Date]

Office of Regional Operations (HFC-100)
5600 Fishers Lane
Rockville, MD 20857

Re: Electronic Signatures

Dear Sir or Madam:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that [Company Name], [Company Address], intends that electronic signatures executed by our employees, [List of employee names] are the legally binding equivalent of traditional hand-written signatures.

Sincerely yours,

[Hand-written signature]

[Name of Company Representative]
[Company Representative Title]

[Employee Name #1]: _____ [Hand-written signature of employee #1]

[Employee Name #2]: _____ [Hand-written signature of employee #2]

[Employee Name #3]: _____ [Hand-written signature of employee #3]

[etc]

**SAMPLE LETTER #2**

[Company Letterhead]

[Today's Date]

Office of Regional Operations (HFC-100)
5600 Fishers Lane
Rockville, MD 20857

Re: Electronic Signature Certificate Statement

To Whom It May Concern:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that [Company Name], intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional hand-written signatures.
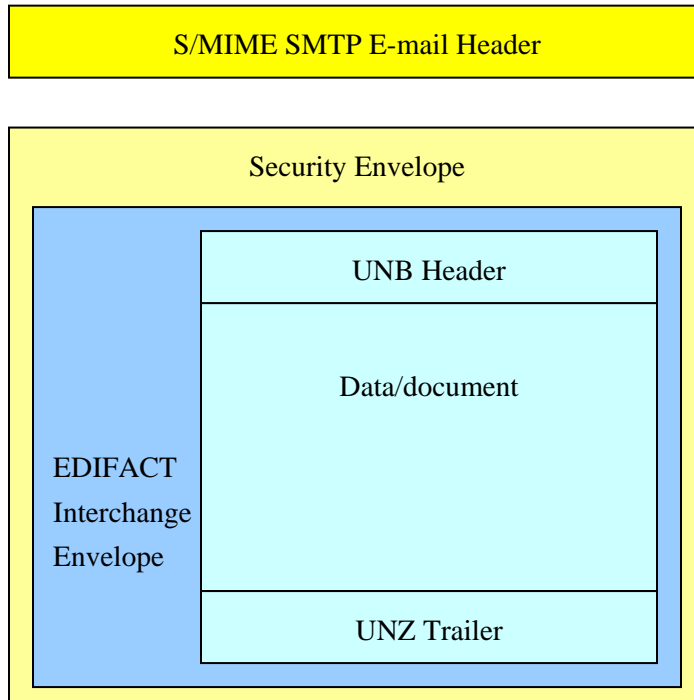
Sincerely yours,

[Hand-written signature]

[Name of Company Representative]
[Company Representative Title]

## APPENDIX I.    EDIFACT Message Structure

**Required message structure (EDIFACT)**

S/MIME SMTP E-mail Header

Security Envelope

UNB Header

Data/document

EDIFACT
Interchange
Envelope

UNZ Trailer

Example: UNB+UNOB:1+016968919:01+FDA:ZZ+060310:0127+37' ——▶ **Header**

SGML document —————————————▶ **SGML Document**

'UNZ+1+37' ————————————▶**Trailer**

**EDIFACT UNB Header Information**

| Description | Code | Comments |
|---|---|---|
| Identification of the start of the UNB header | UNB | The code for the start of the UNB header should be UNB in upper case letters |
| Version of the standard of the UNB header | UNOB:1 | The current version code should be UNOB in upper case letters |

| Description | Code | Comments |
|---|---|---|
| Interchange sender identification code and sender code qualifier | xxxxxxx:01 (for AS1 and AS2 submissions this should match the routing ID) | xxxxxxx should be the number assigned to your company by Dun and Bradstreet Information Services. (For industry sending to the FDA, the sender code qualifier is 01.) |
| Interchange recipient | FDA:zz | xxxx should be the code for the receiving center (CDER, CBER, CDRH, CVM, CFSAN) |
| Date and time of preparation | yymmdd:hhmm | For now, a two-digit designation should be used for the year |
| Interchange control reference | Up to 14 alphanumeric characters | You should assign a unique reference number for each interchange. Otherwise the system will not recognize the transmission as new |

**UNZ Trailer Information**

| Description | Code | Comments |
|---|---|---|
| Identification of the start of the trailer | UNZ | The code for the start of the trailer is UNZ in upper case letters |
| Interchange control count | Up to 6 numerical characters | Counts either the number of messages or the number of functional groups within the interchange. Usually, this is 1 |
| Interchange control reference | Up to 14 alphanumeric characters | This should be the same as the interchange control reference in the UNB header |

EDI headers and trailers are made up of a series of data elements separated by plus (+) signs. A colon should separate segments of the individual data elements. An apostrophe should be used to terminate the header, body of the message, and the trailer.